39. (Added) An antigen specific antibody of a non-human species wherein one or more framework amino acid residues that do not influence CDR presentation are replaced with corresponding residues from Old World Ape.

REMARKS

Claims 1, 3-31 are pending in this application. Claims 8-31 are withdrawn from consideration, as they are drawn to non-elected subject matter. Claims 1 and 3-7 stand rejected. None of the claims stand objected to. Applicant herein amends Claim 1, cancels claims 5 and 7, and adds claims 32-39 to clarify the present invention. Applicant has amended the specification to update the status of the parent application and remove any references to hyperlink or other browser-executable code. These amendments find support in the as-filed specification and claims. No new matter is introduced by the above amendments to the specification or the claims.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Information Disclosure Statement:

The Examiner noted in the Office Action that the IDS filed on July 16, 2001 was submitted with only one page although the PTO-1449 form indicates that it is page 1 of 2. Applicant apologizes for this error, which was committed inadvertently and without intent to deceive. The PTO-1449 form should have stated page 1 of 1, and Applicant resubmits a corrected copy of this page with this response.

In the Specification:

Applicant has amended the specification, per the Examiner's request, to update the status of parent application number 09/300970 and to remove any references to hyperlink or other browser-executable code.

In the Claims:

35 U.S.C. § 112, Second Paragraph

Claims 1 and 3-7 stand rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicant's regard as the invention. In particular, the Examiner alleges that claims 1, and 3-7 are indefinite for reciting the language "derived from," which the Examiner regards as "not clear."

Applicant respectfully disagrees and submits that the term "derived from" has a meaning well known to those of skill in the art. The term "derived from" with respect to complementarity-determining regions (CDRs) and frameworks from antibodies has been described and used in several publications in the art including, Lin (U.S. Patent No. 5,861,155), Tempest, *et al.* (U.S. Patent No. 6,500,931), Owens, *et al.* (U.S. Patent No. 6,407,214), Blackburn, *et al.* (U.S. Patent No. 6,391,299), and Holmes, *et al.* (U.S. Patent No. 6,365,154).

Moreover, the Applicant teaches, at page 5, lines 22-29, that a donor antibody is an antibody that contributes the nucleic acid sequence of its variable CDRs or other functional fragments or analogs thereof to an engineered antibody so as to provide the engineered antibody the antigenetic activity of the donor antibody. Furthermore, the Applicant teaches at page 5, lines 30-37 that acceptor antibodies contribute a portion or all of the nucleic acid sequence encoding the heavy and/or light chain and variable and/or constant region to an engineered antibody. Lastly, the Applicant discloses on page 6, lines 3-8 that an analog is an amino acid sequence modified by at least one amino acid residue either chemically or by substitution. These descriptions can be understood by one skilled in the art to describe a CDR and framework derived from another antibody.

However, solely to facilitate prosecution, and in no way acquiescing to the Examiner's rejection, the Applicant has amended the claims to clarify the scope of the claims. Amended claim 1 no longer recites that CDRs are derived from antigen specific donor antibodies. In addition, the claim now recites that the residues comprising the framework of the claimed antibody are from Old World Ape antibodies. The Applicant respectfully submits that, in view of the forgoing remarks and the claims as amended, the Applicant has overcome the Examiner's rejection under 35 U.S.C. §112, second paragraph, and that this rejection should be withdrawn.

Claim 6 is directed to an antibody of claim 1 wherein the constant regions are from human or Old World Ape. Applicant defines the acceptor antibody as contributing the heavy or light chain framework and/or constant regions to the engineered antibody. See page 5, lines 30-36 of the specification. In addition, Applicant discloses replacing solvent exposed residues of the engineered antibody with the corresponding residues from human. See page 10, lines 6-12. Applicant respectfully submits that claim 6 is fully supported in the specification as the constant region is described as part of the acceptor framework. In addition, as Applicant has amended claim 1 from which claim 6 depends, any rejection based on indefiniteness should be withdrawn.

Claims 5 and 7 have been cancelled therefore rendering the rejection moot. The rejection of claims 3-4 and 6 should be withdrawn as they depend from claim 1.

The Examiner also alleges that claim 7 is indefinite for reciting "one or more solvent-exposed framework residues are replaced with corresponding residues from that homologous selected non-human primate framework." In particular, the Examiner alleges that it is not clear which framework residues are being replaced, whether they are from the donor or acceptor species, or how they are selected.

Applicant has cancelled claim 7, therefore rendering this rejection moot. Applicant has added claims 32-39 to the present application.

Claim 32 is directed to an antibody of claim 1 in which amino acid residues in the engineered antibody are replaced with the corresponding residue from the donor framework. Support for this claim can be found in several examples in the specification, including Example 5 (page 17, line 39-41 and page 18, lines 1-6 and 17-29), Example 6 (page 19, lines 35-38 and page 20, lines 1-8 and 29-40), and Example 8 (page 22, lines 30-36 and page 23, lines 1-4 and 27-38). In each Example noted above, amino acid residues from the engineered antibody were replaced with the corresponding residues from the donor framework.

Claim 33 is directed to an antibody of claim 1 in which amino acid residues in the engineered antibody that may influence CDR presentation are replaced with the corresponding residue from the donor framework. Support for this claim can be found in several examples in the specification, including Example 5 (page 17, line 39-41 and page 18, lines 1-6 and 17-29), Example 6 (page 19, lines 35-38 and page 20, lines 1-8 and 29-40), and Example 8 (page 22, lines 30-36 and page 23, lines 1-4 and 27-38). In each Example noted above, amino acid residues from the engineered antibody were replaced with the corresponding residues from the donor framework.

Claim 34 is directed to an engineered antibody in which one or more solvent–exposed acceptor framework residues are replaced with corresponding residues from a human framework. Support for this claim can be found in the description of the replacement of solvent exposed residues of the engineered antibody with the corresponding residues from the human V region. See page 10, lines 6-12 and the reference to U.S. Patent No. 5,639,641.

Claim 35 is directed to an antibody of claim 1 in which the Old World Ape acceptor framework comprises at lest one analog amino acid. This claim is supported in the

specification at page 6, lines 3-8. Applicant provides a definition of analog to an amino acid sequence.

Claims 36-38 are directed to the antibodies presented in Examples 5, 6, and 8, respectively of the specification. Support for newly added claim 36 can be found on page 18, lines 7-8 and 29-30 as well as in SEQ ID NOs: 68 and 70 of the sequence listing. Support for newly added claim 37 can be found on page 20, lines 5-7 and 40 and page 21, line 1 as well as in SEQ ID NOs: 73 and 74 of the sequence listing. Support for newly added claim 38 can be found on page 23, lines 4-6 and 38-39 as well as in SEQ ID NOs: 77 and 78 of the sequence listing.

Claim 39 is directed to antigen specific antibody of a non-human species in which residues of the framework that do not influence CDR presentation are replaced with the corresponding residues from Old World Ape. Support for this claim can be found in several examples in the specification including Example 5 (page 17, line 39-41 and page 18, lines 1-6 and 17-29), Example 6 (page 19, lines 35-38 and page 20, lines 1-8 and 29-40), and Example 8 (page 22, lines 30-36 and page 23, lines 1-4 and 27-38). In these Examples, Applicant teaches the comparison of amino acid sequences from non-human antigen binding antibodies with amino acid sequences of corresponding Old World Ape antibodies. Based on a predictive three-dimensional structural determination, the amino acids of one antibody are replaced with the other to produce an engineered antibody. Applicant also discloses the replacement of residues of an engineered antibody with the corresponding residues from the human V region. See page 10, lines 6-12. This claim is directed to replacing residues in the framework of an antibody with corresponding Old World Ape amino acid residues, thus, leaving the amino acid residues that do influence CDR presentation as wild type.

Applicant respectfully submits that in view of the forgoing remarks and the claims as amended, the Applicant has overcome the Examiner's rejection under 35 U.S.C. §112, second paragraph, and that this rejection should be withdrawn.

35 U.S.C. § 112, first paragraph

Claims 1 and 3-7 stand rejected under 35 U.S.C. 112, first paragraph as not being enabling. While the Examiner has conceded that the specification is enabling for an isolated antibody comprising all six CDRs from a non-human donor in a an acceptor that is from *Pan troglodyte*, the Examiner alleges that it does not provide enablement for an antibody comprising any derived donor CDRs wherein the donors have deletions, replacements, or insertions. The Examiner cites Rudikoff, *et al.* (*Proc Natl Acad Sci USA* 79:1979-1983 (1982)) as teaching that a single amino acid replacement in the CDR of phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. In addition, the Examiner also cites Panka, *et al.* (*Proc Natl Acad Sci USA* 85:3080-3084 (1988)) as demonstrating that a single amino acid substitution of "serine to alanine" can result in decreased affinity and Amit, *et al.* (*Science* 233:747-753 (1986)) as demonstrating that the substitutions of residues in the framework of an antibody can effect binding affinity. The Examiner alleges that the predictability of binding ability after a single mutation in the CDR is variable and predictable.

Applicant has amended claim 1 to recite that all six CDRs of the claimed antibody are from an antigen-specific donor antibody. Applicant submits that the enablement provision of 35 U.S.C. § 112, first paragraph ensures that one skilled in the pertinent art will be able to make and use the claimed invention without undue experimentation, *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.* 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), but it does not require the inventor to disclose what is already known in the art, *Spectra-Physics, Inc. v. Coherent, Inc.* 3 U.S.P.Q.2d. 1737, 1743 (Fed. Cir. 1987), *cert. denied,* 484 U.S. 954 (1987). Enablement is

not precluded by a necessity for some experimentation, such as routine screening. Thus, the key word is "undue" not "experimentation." *In* re *Wands*, 8 U.S.P.Q.2d. 1400, 1404 (Fed. Cir 1988). See also *Amgen, Inc. v. Chugai Pharmaceuticals, Inc.*, 18 U.S.P.Q.2d. 1016, 1027 (Fed. Cir. 1991). In fact a considerable amount of experimentation is permissible if it is routine or if the specification provides guidance in conducting the experimentation. *In re Wands*, 8 U.S.P.Q.2d. at 1404.

Applicant respectfully submits that if claim language defines the invention with a reasonable degree of particularity and distinctness, a claim may be drawn as broadly as the prior art permits. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 225 U.S.P.Q. 634, 641 (Fed. Cir. 1985) ("If the claims, read in light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more."), *cert. dismissed*, 474 U.S. 976 (1985); MPEP § 706.03(d).

Applicant has disclosed antibodies comprising CDRs from an antigen-specific donor antibody of a non-human and a framework Old World Ape antibody. As the Examiner notes, the Applicant has provided examples in which CDRs from rat anti-IL-5, murine anti-integrin and murine anti-erythropoietin antibody were successfully grafted to a *Pan troglodyte* framework and produced functional antibodies. In addition, Applicant has provided methods for replacing selected amino acid residues in the engineered antibody that are predicted to influence CDR presentation. See Example 5 (page 17, line 39-41 and page 18, lines 1-6 and 17-29), Example 6 (page 19, lines 35-38 and page 20, lines 1-8 and 29-40), and Example 8 (page 22, lines 30-36 and page 23, lines 1-4 and 27-38). Selection of the residues to be replaced in the framework of engineered antibodies are based on conserved regions that are structurally known to influence CDR binding. Although a comparison of the non-human

CDR regions and the acceptor framework will differ based on the acceptor and donor antibodies used to produce the engineered antibody, Applicant has demonstrated that non-human CDRs can be successfully grafted to a *Pan troglodyte* acceptor framework and that the functionality of this engineered antibody can be improved by replacing the homologous residues from the donor antibody into the acceptor framework.

In addition, the cited references do not demonstrate that amino acid substitutions in the variable or structural regions of an antibody will create an unpredictable affinity for an antigen. Rudikoff, *et al.* suggest that the introduction of somatic mutations in antibodies will affect binding affinity. This hypothesis is based on the observation that somatic mutations do produce antibodies with varying binding affinity. Comparison of mutant chains with wild type indicate differences that were likely to affect binding affinity. See page 1981. Furthermore, Panka, *et al.* and Amit, *et al.* both contribute to a developing data bank of residues known to affect binding affinity. They do not suggest that mutants in the antibody framework will always create an unpredictable effect. Rather, they suggest that information from crystallographic analysis can be used to guide the predictability of mutations on antigen/antibody binding. See Panka, *et al.* at page 3084.

With respect to claim 6, Applicant has amended claim 1 to recite that all six CDRs are from an antigen-specific antibody. Constant regions are part of the acceptor framework and, as discussed above, are more predictably replaced in an engineered antibody.

Claims 5 and 7 have been cancelled therefore rendering the rejection moot. The rejection of claims 3-4 and 6 should be withdrawn as they depend from claim 1.

Applicant respectfully submits that, in view of the forgoing remarks and the claims as amended, Applicant has overcome the Examiner's rejection under 35 U.S.C. §112, first paragraph, and that this rejection should be withdrawn.

35 U.S.C. § 103

Claims 1 and 3-7 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Newman, *et al.* (U.S. Patent No. 5,756,096) in view of Vijh-Warrier, *et al.* (*Molecular Immunology* 32:1081-1092) and Adair, *et al.* (WO 91/09967, published 7/11/91). In particular, the Examiner alleges that Newman, *et al.* teach a primatized antibody comprising the variable domain from monkey and the human IgG1 constant region as well as a framework from chimpanzee (column 2, lines 1-10). However, the Examiner concedes that Newman, *et al.* do not teach or suggest the use of *Pan troglodyte* framework or the replacement of solvent exposed framework.

The Examiner alleges that Vijh-Warrier, *et al.* teach the nucleotide and amino acid sequences of various *Pan troglodytes* and that Adair, *et al.* teach a method of CDR grafting as well as non-CDR residues that contribute to antigen binding. Thus, the Examiner alleges that it would have been obvious to one skilled in the art to produce an antibody comprising CDRs from non-human species and an acceptor framework from *Pan troglodytes* wherein the solvent exposed framework residues are replaced with corresponding residues from a non-human primate.

The Examiner alleges that Newman, *et al.* teach that human and chimpanzee constant regions are similar (column 4, lines 2-4). In addition, the Examiner alleges that Vijh-Warrier, *et al.* teach that chimpanzee Mabs are not likely to elicit deleterious response in humans (see page 1089). Finally, the Examiner suggests that Adair, *et al.* teach replacing solvent exposed framework. (pages 20-23, 38-39 and Figure 3).

Applicant respectfully traverses these rejections. For a proper obviousness rejection under 35 U.S.C. §103, the Examiner has the burden of establishing *prima facie* with evidence or reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the

combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaek*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

Applicant's invention is directed to engineered antibodies in which a known antigen-specific binding region from a non-human species is associated with an acceptor framework from Old World Ape. Applicant has specified that the acceptor framework is preferably from Old World Ape which differs significantly from the Old World Monkey acceptor framework, which is disclosed in Newman, *et al.* Therefore, the acceptor framework proposed by the Applicant differs from that used by Newman, *et al.* and is not an obvious substitute. Newman, *et al.* point out that the invention patented is based on using an antibody framework from monkeys, which is evolutionarily distant from humans, rather than the similar *Pan troglodytes* genus (see column 2, lines 19-25). This motivation indicates that Newman, *et al.* teaches away from using *Pan troglodytes* because they were interested in using an evolutionarily distinct framework to avoid human anti-antibody response.

Vijh-Warrier, *et al.* disclose using chimpanzees to create antibodies for passive immunization in humans. They do not teach or suggest the use of an Old World Ape framework in combination with the CDRs from a non-human antigen binding antibody. In addition, they do not teach or suggest creating an engineered antibody using CDRs and framework residues from different species. Finally, they do not teach or suggest that frameworks residues from Old World Ape antibodies can be successfully used in an engineered antibody.

Furthermore, while Adair, *et al.* suggest some specific residues in humanized antibodies that are conserved for binding, they do not teach or suggest the combination of non-human antigen binding regions with an acceptor framework from Old World Apes. Adair, *et al.* disclose humanized antibodies and methods of humanizing antibodies. They do not teach or suggest the use of Old World Ape framework. In addition, they do they teach or suggest the comparison of residues from a non-human donor antibody with the corresponding residues from an acceptor antibody to produce homologous replacements in order to improve binding.

The Examiner is using hindsight reconstruction to provide the motivation to combine the references which make up the above rejections, rather than interpreting the prior art as a whole, from the point of view of a person having ordinary skill in the art at the time the invention was made, as required by 35 U.S.C. §103. His current conclusion that the instant invention is obvious could only be reached from the benefit of the teachings of the instant specification. Applicant submits that within the four corners of these references, there is nothing which teaches or suggests their particular combination. It is well-founded patent law that such hindsight reconstruction is an impermissible way to arrive at a conclusion of obviousness. *Hodosh v. Block Drug Co.*, Inc., 220 U.S.P.Q. 182, 187 (Fed. Cir. 1986).

Similarly, with respect to claim 6, none of the references demonstrate combining CDRs from an antigen-binding antibody with the framework of an Old World Ape. In addition, they do not teach or suggest that in such an engineered antibody the constant region may be from human or Old World Ape.

Claims 5 and 7 have been cancelled therefore rendering the rejection moot. The rejection of claims 3-4 and 6 should be withdrawn as they depend from claim 1.

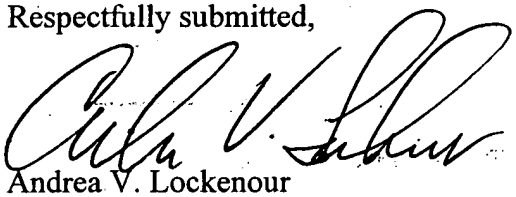
Applicant respectfully submits that in view of the forgoing remarks and the claims as amended, the Applicant has overcome the Examiner's rejection under 35 U.S.C. §103(a), and that this rejection should be withdrawn.

Applicant reserves the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. Applicant thanks the Examiner for the Office Action and believes this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned agent.

Attached hereto is a marked-up version of the changes made to the current amendment and is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 1, please replace the paragraph at lines 4-5 with the following paragraph:

--This application claims the benefit of U.S. Provisional Application No. 60/083,367, filed April 28, 1998 now abandoned.--

At page 9, please replace the paragraph at lines 28-36 with the following paragraph:

--The resulting engineered constructs, in which the donor CDRs are grafted onto primate acceptor frameworks, are subsequently refined by analysis of three-dimensional models based on known antibody crystal structures as found, e.g., in the [Protein Data Bank, http://www.pdb.bnl.gov/pdb-bin/pdbmain] Protein Data Bank (PDB), which is operated by Rutgers, The State University of New Jersey; the San Diego Supercomputer Center at the University of California, San Diego; and the National Institute of Standards and Technology -- three members of the Research Collaboratory for Structural Bioinformatics (RCSB) or a similar data bank containing three-dimensional protein structures. Alternatively, computer generated three-dimensional models of the donor antibody may be computed by means of commercially available software such as "AbM" (Oxford Molecular, Oxford, UK).--

At page 12, please replace the paragraph at lines 6-12 with the following paragraph:

--The chimpanzee VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences in computer homology searching of the Kabat database of Sequences of Proteins of Immunological Interest [(ftp://ncbi.nlm.nih.gov/repository/kabat/)]provided through the National Center for Biotechnology Information, which is operated by the National Library of Medicine and the National Institute of Health. The results of this analysis are shown in Table 1.--

In the Claims

1. (Amended) An antibody comprising six complementarity determining regions (CDRs) [derived]from an antigen specific donor antibody of a non-human species and acceptor framework comprising amino acid residues [derived]from an Old World Ape.